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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,608	KULAKSIZ ET AL.	
	Examiner	Art Unit	
	GARY W. COUNTS	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4, 15, 16, 25-28 amd 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *27,28 and 30* is/are allowed.

6)☒ Claim(s) *1, 4, 15, 16, 25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed 09/17/09 is acknowledged and has been entered. Currently, claims 1, 4, 15, 16, 25-28 and 30 are pending. Claims 27, 28 and 30 are considered allowable. Claims 1, 4, 15, 16, 25 and 26 are under examination.

Withdrawn Rejections

All rejections of claims not reiterated herein, have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 4, 15, 16, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining

undue experimentation are set forth in *In re Wands* USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to a method for diagnosing a disease characterized by non-physiological levels of hepcidin, comprising obtaining a tissue or fluid sample from a subject contacting the sample with an antibody or fragment thereof that specifically binds to one or more carboxy terminal epitopes contained within amino acids 70-84 of SEQ ID NO: 2, and quantifying hepcidin level in the sample; wherein: the disease is selected from the group consisting of chronic renal insufficiency, renal anemia and hereditary hemochromatosis; the tissue or fluid sample is selected from the group consisting of kidney samples, liver samples, and urine samples and the non-physiological level of hepcidin is indicative of the disease.

The specification fails to properly provide adequate written description to enable the methods as claimed. The specification on page 9 discloses that the physiological concentration of hepcidin in blood is in the range of about 50 to about 150 ng/ml and that nonphysiological concentrations are below or over this range. However, the specification does not provide physiological or non-physiological levels of hepcidin in urine, liver or kidney samples nor does the specification disclose a correlation of urine, liver or kidney sample levels with chronic renal insufficiency, renal anemia or hereditary hemochromatosis. There is no data or results provided which show a correlation of hepcidin obtained from a kidney sample, liver

sample or urine sample wherein an antibody which specifically binds to one or more carboxy terminal epitopes contained within amino acids 70-84 of SEQ ID NO: 2 is used to detect hepcidin and used to diagnose chronic renal insufficiency, renal anemia and hereditary hemochromatosis. Further, there is no evidence such as graphs or statistical values which provide a correlation of hepcidin levels compared to standards or controls. The only examples for detecting prohepcidin in human were directed to a sensitive ELISA which detected prohepcidin in serum of patients with hereditary hemochromatosis, chronic renal insufficiency and renal anemia (e.g. p. 11, lines 25-27, p. 49). However, the specification discloses that the C-terminal antibody EG(1)-HepC showed no immunoreactivity in this ELISA assay (e.g. p. 55). Thus, the specification only appears to provide significant results in serum using an antibody directed to N-terminal epitopes of hepcidin for diagnosing hereditary hemochromatosis, chronic renal insufficiency and renal anemia.

Also according to Strongin (Laboratory Diagnosis of Viral Infections, Sensitivity, Specificity, and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications, Lennette, ed., Marcel Dekker, Inc., New York, pp.211-219, 1992) a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the following: (1) the sensitivity of the assay; (20 the true-positive test rate: (3) the false-negative test rate; (4) the specificity, or percentage of patients without the disease who will display a negative result; (5) the true-negative test rate; (6) the false-positive test rate; (7) the predictive value, or the probability that the test result is correctly indicating the presence or absence of the disease; (8) the prevalence, or number of patients in any given population that have the

disease in question; (9) the efficiency or percentage of all results that are true; (10) the accuracy of the recited diagnostic assay.

Additional consideration must also be examined to enable the clinician to practice the invention, including assessment of the following: (1) when is the maximum sensitivity desired? (2) when is the maximum specificity desired?; (3) when is the maximum efficiency desired?; (4) how is the maximum sensitivity or specificity achieved?; (5) how is the predictive value maximized? An essential understanding of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test. Therefore, how can one of ordinary skill in the art positively diagnose chronic renal insufficiency, renal anemia and hereditary hemochromatosis using an antibody which specifically binds to one or more carboxy terminal epitopes contained within amino acids 70-84 of SEQ ID NO: 2 if one does not know what is a nonphysiological level or if a correlation exits between a level and kidney, liver or urine samples and chronic renal insufficiency, renal anemia and hereditary hemochromatosis. Further, if one does not know physiological levels how would one determine an increase or a decrease in level of or if the increase or decrease would correlate with the disease. Thus the specification does not enable one skilled in the art to positively diagnose chronic renal insufficiency, renal anemia and hereditary hemochromatosis as claimed and one cannot practice the claimed method without undue experimentation.

Response to Arguments

2. Applicant's statements and arguments filed 09/17/09 have been fully considered but they are not persuasive.

Applicant argues that the Examiner rejected the claims based on the enablement requirement under 35 USC 112 first paragraph mainly upon the following assertions:

1) the claims do not include the specific range of non-physiological level of hepcidin.

2) the specification does not provide graphs or statistical values which provide a correlation of hepcidin levels compared to standards or control.

3) the only examples for detecting prohepcidin in human were directed to a sensitive ELISA, but the C-terminal antibody EG(1)-HepC showed no immunoreactivity in this ELISA assay.

4) the specification does not enable one skilled in the art to positively diagnose the disease as claimed because of lack of knowledge on physiological levels of hepcidin.

The Examiner acknowledges these statements. However, the Examiner would like to note particularly that the Examiner has not relied upon the claims in the enablement rejection (1 note above) but rather has stated that the specification does not provide guidance on physiological or non-physiological levels of hepcidin in urine, liver or kidney samples. Also, with respect to Applicant's second statement, of hepcidin levels compared to standards or controls the enablement rejection is based on the specification not teaching a correlation of hepcidin obtained from a kidney sample, liver sample or urine sample and providing a diagnosis of chronic renal insufficiency, renal anemia and herediatary hemochromatosis. With respect to the statement of lack of knowledge on physiological levels of hepcidin. The enablement rejection has not been solely based on just physiological levels of hepcidin but more precisely on the fact that the specification does not provide guidance on physiological or non-physiological levels of hepcidin in urine, kidney or liver samples and has not provided a

correlation of levels in the samples to render or show a diagnosis of chronic renal insufficiency, renal anemia and hereditary hemochromatosis..

Applicant argues that the evidence of how to practice the claimed invention can convince a person of ordinary skill in the art that the diagnostic method would work to aid a clinician to determine whether the disease is present. This argument is not found persuasive because it is unclear how the method would aid a clinician if the method has not been shown to work or provide a correlation to chronic renal insufficiency, renal anemia and hereditary hemochromatosis. As stated above and in the previous office action the specification fails to provide guidance on physiological and non-physiological levels of hepcidin in urine, liver and kidney samples or a correlation of these levels with chronic renal insufficiency, renal anemia and herediatary hemochromatosis. Further, the specification fails to provide results, data or evidence that such samples provide physiological and non-physiological levels which are correlated to or with chronic renal insufficiency, renal anemia and herediatary hemochromatosis. Therefore, for reasons stated above and in the previous office action the rejection is maintained.

Allowable Subject Matter

3. Claims 27, 28 and 30 are considered allowable.

4. The following is a statement of reasons for the indication of allowable subject matter: The prior art of record neither teaches nor suggests a method for detecting hepcidin as recited wherein the antibody or fragment thereof specifically binds to one or more carboxy terminal epitopes contained within amino acids 70 to 84 of SEQ ID NO. 2.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/

Examiner, Art Unit 1641

/Melanie Yu/
Primary Examiner, Art Unit 1641